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Patch Me If You Can!

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Disclosure

- Research and Educational Grants
  - Baxter
  - Genentech
  - Dyax
  - Merck
- Speaker's Bureau
  - Baxter

Objectives

1. Recognize important contact allergens in cosmetics, metals etc.
2. Develop a current understanding of patch testing to these allergens

A Sneak Preview on the
Update on Practice Parameters for Contact Dermatitis
2013?

SUMMARY STATEMENT: The clinician should also consider cosmetics and personal hygiene products as a source of potential allergens in patients with dermatitis occurring in sites other than the site of application.

Ectopic CD

Patterns of Cosmetic Contact Allergy

- Facial cosmetic dermatitis
  - Bilateral & patchy
  - Gold: dermatitis in women who wear cosmetics with titanium dioxide
- Eyelid
  - Nickel transferred to the eyelid by fingers
  - Cocamidopropyl betaine (surfactant in shampoo) can present with eyelid dermatitis alone
- Neck
  - "run-off" pattern from cosmetics applied to face, scalp or hair often initially affect the neck
  - Most affected site of ACD from nail varnish is the neck Toluene sulfonamide formaldehyde resin in nail polish
- Lips
  - Consort/Connubial Dermatitis: primarily fragrance

COSMETICS

- Average adult apply 12 personal hygiene products daily
- These 12 products exposes one to 168 discrete chemicals
- Combined with "home-brewed" remedies, the number of cosmetics available are almost endless

SUMMARY STATEMENT : When evaluating allergic contact dermatitis from cosmetics and personal care products which contain considerable numbers of chemical ingredients, consider that the most common causes are due to a few important chemical classes including fragrances, preservatives, excipients, nickel and sun blocks

Top 10 (+) reactions to NACG Allergens	NACD 2009-10	TT
Nickel Sulfate (Metal)	15.5	x
Neomycin (Antibiotic)	8.7	x
Fragrance Mix I (Fragrance)	8.5	x
Bacitracin (Antibiotic)	8.3	x
Balsam of Peru (Fragrance)	7.2	x
Cobalt Chloride (Metal)	6.2	x
Quarternium 15 (Preservative)	5.8	x
Formaldehyde (Preservative)	5.8	x
PPD	5.5	x
Fragrance Mix II (Fragrance)	4.7	

Warshaw EM et al. North American Contact Dermatitis Group Patch Test Results for 2009-2010. DERMATITIS, March/April 2013. Vol 24: 2:50-59

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TRUE TEST vs. NACDG

Of the top 40 NACDG allergens, the following antigens are not on TRUE Test:

- Fragrance mix II (fragrance) (4.7%)
- Iodopropynyl butylcarbamate (preservative) (4.3%)
- Propylene glycol (humectant & stabilizer) (3.2%)
- Propolis (excipient) (2.1%)
- Dimethylaminopropylamine (surfactant) (2.0%)
- Hydroxyethyl methacrylate (2.0%)
- Oleamidopropyl dimethylamine (surfactant) (1.8%)
- Shellac (eye or lip products) (1.7%)
- Decyl glucoside (surfactant) (1.5%)
- Cocamidopropyl betaine (surfactant) (1.4%)
- Majantole (flavoring/fragrance) (1.4%)
- ylang ylang oil (flavoring/fragrance) (1.3%)
- Carvone (flavoring/fragrance) (1.1%)
- DMDM hydantoin (preservative) (1.0%)
- Mixed dialkyl thioureas (rubber manufacturing) (1.0%)

(%) frequency of positive reaction in NACD 2009-2010

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Fragrance

Fragrance Mix I	Balsam of Peru *Myroxylon pereirae*	Fragrance Mix II
Cinnamic alcohol 1%	Cinnamic acid	Coumarin 2.5%
Cinnamic aldehyde 1%	Benzoyl Cinnamate	Hydroxyisohexyl 3-cyclohexene carboxaldehyde (Lyral) 2.5%
α-Amyl cinnamaldehyde (amyl cinnamal) 1%	Benzoyl Benzoate	Citronellol 0.5%
Hydroxycitronellal 1%	Benzoic acid	Farnesol 2.5%
Geraniol 1%	Vanillin	Citral 1.0%
Isoeugenol 1%	Nerodilol	α Hexyl cinnamic aldehyde 5.0%
Eugenol 1%		
Oak moss 1%		

Other fragrance sensitizers: Lyral, jasmine, lavender, sandalwood, tea tree oil , ylang ylang oil, lemongrass oil, jasmine, Narcissus

Fragrance mix I & Balsam of Peru (in TT) pick up 60-70% of all ACD to fragrances at best

Fragrance Mix Patch Test

- Low specificity
  - Mild Irritant, caution with weak (+) reactions
- Increased probability of a relevant FM patch-test
  - Increased strength of test reaction
  - Repeated (+) reaction on retest
  - (+) to one of its ingredients

Devos SA et al. Relevance of Positive Patch-Test Reactions to Fragrance Mix. Dermatitis, Vol 19, No 1, 2008: 43–47

FDA Voluntary Cosmetic Registration Program Database

- ~ one in six stay-on cosmetics & one in four rinse-off products contain a formaldehyde releaser
  - frequency
    - imidazolidinyl urea (7%)
    - DMDM hydantoin (5.4%)
    - Diazolidinyl urea (4.5%)
    - quaternium-15 (1.4%).

de Groot, White et al. 2010
de Groot, Flyvholm et al. 2009

Cosmetic Preservatives

Formaldehyde	(+) PT*	Non Formaldehyde	(+) PT
Formaldehyde	5.8 %	Iodopropynylbutylcarbamate	4.3%
Quarternium 15	5.8%	Methyldibromoglutaronitrile (Euxyl K 400)	3.8 %
Diazolidinyl urea (Germall II)	2.2 %	MCI/MI	2.5 %
Imidazolidinyl urea (Germall)	2.2 %	Parabens	0.8 %
Bromonitropropane (Bronopol)	1.0 %	Chloroxylenol	0.5 %
DMDM Hydantoin (Glydant)	1.0 %		

Paraben, quarternium-15 & formaldehyde preservatives are frequently combined & cosensitize **

* % Prevalence PT reaction based on NACDG 2009-2010
**Albert MR et al. Concomitant positive reactions to allergens in the patch testing standard from 1988-1997. Am J Contact Dermat 1999; 10:219-223
Warshaw EM et al. North American Contact Dermatitis Group Patch Test Results for 2009-2010. DERMATITIS, March/April 2013, Vol 24: 2;50-59

Formaldehyde

Most common potential source of exposure

- Cosmetics
  - Rarely on ingredient label, direct use forbidden in some countries
  - Contain formaldehyde releasers
- Permanent press textiles
  - Increase strength, prevent shrinking, resist wrinkling (permanent press) of cellulose and rayon fibers

Agner et al.Formaldehyde allergy: a follow up study. Am J Contact Dermatitis 1999;10:12-17

Formaldehyde Resins

- Dermatitis pattern in areas where clothing fit tightly
  - Posterior neck, upper back, lateral thorax, anterior & posterior axillary folds (spares axillary vault), waistband (spares undergarment areas), flexor
- Importance of pressure, friction, heat, perspiration

Treatment for Formaldehyde Resin Allergic Contact Dermatitis

- **Use 100% silk, polyester, acrylic, nylon**
  - Linen & denim if soft & wrinkle easily
- **Avoid "easy care," "permanent press," or "wrinkle free"**
- **Some also recommend avoidance of formaldehyde-releasing preservatives in personal products***
- **AVOID FORMALDEHYDE RESINS AT ALL TIMES. Occasional exposure to "Dress clothes" on weekends is enough to maintain dermatitis**

Reich H & Warshaw E. Allergic Contact Dermatitis from Formaldehyde Textile Resins. Dermatitis. 2010; 21:265–76
*Scheman A, Jacob S, Zirwas M, et al. Contact allergy: alternatives for the 2007 North American Contact Dermatitis Group (NACDG) standard screening tray. Dis Mon 2008;54:7–156.

Non formaldehyde releaser preservatives

- **Methlydibromo gluteronitrile (sensitizer in Euxyl K 400)**
- **11.8% of hand dermatitis associated with Euxyl K 400 were occupation related**
  - **solvents, oils, lubricants, fuels**
- **In cosmetics, ACD from Euxyl K 400 or its components is most commonly reported in hand and face lotions, cosmetics, hair products, ultrasonic gels**

Warshaw, Buchholz et al. 2009
Diepgen and &Weisshaar. 2007
Warshaw, Ahmed et al. 2007

SUMMARY STATEMENT : Patients suspected to have allergy to hair products should be evaluated for PT reactions to
- cocamidopropyl betaine,
- paraphenylenediamine, and
- glycerol thioglycolate.

Cocoamidopropyl betaine Contract Allergen of 2004

- Amphoteric surfactant often found in shampoos, bath products, eye & facial cleaners, liquid detergents, surface cleaners, pet care products, other skin and hair care, liquid shower gels, roll-on deodorants, and facial cleansers
- Second most common allergen in shampoo
- Less irritating but more sensitizing than older polar surfactants (sodium lauryl sulfate)
- Positive reactions to this allergen are often clinically relevant

Shampoos

Typically composed of 10-30 ingredients

Table 1. Common Allergens in Shampoos

Allergen	No. of Products Containing Allergen[1]	% of Products Containing Allergen
Fragrance	170/179	95.0
Cocamidopropyl betaine	95/179	53.0
Methylchloroisothiazolinone/methylisothiazolinone	92/179	51.0
Formaldehyde-releasing preservatives	87/179	48.0
Propylene glycol	68/179	38.0
Vitamin E (tocopherol)	51/179	28.0
Parabens	43/179	24.0
Benzophenones	10/179	5.5
Iodopropynyl butyl carbamate	10/179	5.5
Methyldibromoglutaronitrile/phenoxyethanol	6/179	3.0

Of 9 products with no fragrance, 4 had fragrance related potential allergens
(3 had botanical ingredients, 1 had benzyl alcohol)
Thus, only 5 products in database were truly fragrance free & definitely safe for patients with fragrance allergy

Matthew Zirwas and Jessica Moe Shampoos. Dermatitis, Vol 20, No 2 (March/April), 2009: pp 106–110

Shampoos

Table 2. Low-Allergenicity Shampoos

Product	Ingredients
AFM Safe Choice Hair and Body Shampoo*	Purified water, sodium laureth sulfate, cocamide MEA, citric acid
Free & Clear Shampoo†	Purified water, disodium cocamphodiacetate, disodium laureth sulfosuccinate, sodium chloride, cocamidopropylamine oxide, PEG-150 pentaerythrityl tetrastearate, citric acid, PEG-12 dimethicone, disodium EDTA, potassium sorbate

EDTA = ethylenediaminetetraacetic acid; MEA = monoethanolamine; PEG = polyethylene glycol.
*American Formulating and Manufacturing, San Diego, CA.
†Pharmaceutical Specialties, Rochester, MN.

Matthew Zirwas and Jessica Moe Shampoos. Dermatitis, Vol 20, No 2 (March/April), 2009: pp 106–110

P-phenylenediamine (PPD) Contact Allergen of 2006

Permanent Hair Dye

- Theoretically, does not cause reaction if fully oxidized
- In reality, it is likely that PPD is never completely oxidized

New Route of Exposure

- Body painting & temporary tattooing (until stratum corneum is shed)
- Clinical course
  - (1) acute intense eczematous response within 1-2 days of tattooing
  - (2) subacute response: lichenoid eruptions within 1- 2 week
    - Most likely causative agent is PPD
- PPD sensitization is likely lifelong; may react to first attempts at hair coloring

Lao V. p-Phenylenediamine Dermatitis Volume 17, Issue 02, June 2006, Pages 53-55 Hesse et al. Contact Dermatitis to hair dyes in a Danish Adult population: an interview based study. Br J of Dermatol 2005; 153:132-5
Dickel H et al. Comparison of patch test with standard series among white and black racial groups. Am J Contact Dermat 2001;12:77-82

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Types of Hair Dye

- Semipermanent: 2/4 weeks
- Demi-permanent: 6/8 weeks
  - Ammonia-free (cannot lighten hair)
- Permanent: ..forever

PPD-Free Hair Dyes

Wella Koleston Perfect (permanent) *
Wella Color Charm (demipermanent)
Schwarzkopf Igora Royal (permanent) **
Goldwell Color Chic (permanent) ***
Goldwell ReShade for Men (demipermanent)
Sanotint Light (demipermanent) ****
L'Ore`al Paris Excellence To-Go 10-Min. Cre`me Colorant (demipermanent) *****

*The Wella Corporation, Richimond, VA
**Schwarzkopf & Dep, Rancho Dominguez, CA
***Sanotint, Cosval Arese, Italy
****PSS, Inthicum Heights, MD
*****L'Oreal USA Inc, Clark, NJ

Dermatitis. Vol 22, No 4 (July/August), 2011: pp 189–192

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SUMMARY STATEMENT: Suspect allergy to nail products when the dermatitis present locally at the distal digit or ectopically on the eyelids and face.

- Up to 80% appear on the neck, face, lips,eyelids
  - -27% reported in periungual region of the hands and feet
  - unusual locations: gluteal, perianal, genital
- Most ACD to nail polish & artificial nail products are to tosylamide/formaldehyde resin
  - nail polish enamel
  - nail hardeners
  - setting lacquers
- Majority react to water-soluble monomers & dimers of tosylamide/ formaldehyde resin in dry polish
  - some react only to wet polish
- Alternative: alkyl polyester resin

Lazzarini, Duarte et al. 2008
Orton and Wilkinson 2004

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SUMMARY STATEMENT 44: Suspect the diagnosis of photodermatitis to cosmetics when eczema occurs in a light-exposed distribution following the use of a skin care product or cosmetic, including sunscreens . In these cases, photopatch testing must be performed.

Involves
- sun-exposed areas
- face,
- "V" of neck
- dorsal hands and forearms

Spares
- Upper eyelids
- Upper lip
- Submental
- Postauricular areas

Sunscreens

TABLE 2 LEVEL OF PROTECTION FROM DIFFERENT INGREDIENTS

		Sunburn	Increasing risk of melanoma	
Common UV absorbers	Type	UVB	UVAII	UVA I
Octyl methoxycinnamate	Chemical			
Homosalate	Chemical			
Padimate O	Chemical			
Octyl salicylate	Chemical			
2-Phenyl-benzimidazole-5-sulfonic acid	Chemical			
Oxybenzone "(benzophenone-3)"	Chemical			
Menthyl anthranilate	Chemical			
Octocrylene	Chemical			
Avobenzone	Chemical			
Nanosun™ Zinc Oxide	Mineral			
Level of Protection	None	Moderate	Good	Excellent

Chemical absorbers
UVB (290–320 nm)
UVA II (321–340 nm)
UVA I (341–400 nm)

Physical blockers
Titanium Dioxide
Zinc Oxide

What does SPF stand for?

Sun Protection Factor (Measure UVB protection)

- Range from 2-80
- UV radiation it takes to burn skin with sunscreen compared to burn bare skin. (i.e. SPF 30 take 30 x amount of UVB to cause sunburn)
  - Nothing to do with amount of time you can spend in the sun
  - Varies with every individual
- SPF 15 bocks ~95 % UVB rays
  - SPF 30 blocks ~97 %
  - SPF 50 blocks ~98%
  - SPF 100 blocks ~99%
  - none offers 100% protection
  - **Bottom line:** Your daily sunscreen should be somewhere between SPF 30 and 50

Contact Dermatitis to Sunscreen

Allergic and Photoallergic

- Chemical Sun blocks: most common cause of ACD
  - PABA, benzophenone, cinnamates
- Physical UV Blocker
  - Titanium dioxide & zinc oxide: no report of CD or photoallergy

Sun Protection should include
sunscreens
sun-protective clothing
PLUS cautious sun avoidance

Octinoxate 7.5%
Octocrylene 2%
Oxybenzone 3%
Zinc Oxide 6%

Titanium: 5%
Zinc Oxide:10%

Zinc Oxide:18.6%

Titanium:10%
Zinc Oxide:3%

TABLE 3. Body Sites of Dermatitis and Final Diagnoses

Characteristic	Primary, n (%)	Total of Up to 3 Listed,† n (%)
Dermatitis site	n = 4300*	n = 4308
Scattered/generalized	907 (21.1)	1101 (25.6)
Hand	866 (20.1)	1031 (24.9)
Face	667 (15.5)	926 (21.5)
Eyelids	392 (9.1)	466 (10.8)
Trunk	250 (5.8)	505 (11.7)
Leg	201 (4.7)	469 (10.9)
Arm	184 (4.3)	596 (13.8)
Scalp	150 (3.5)	236 (5.5)
Lips	138 (3.2)	181 (4.2)
Foot	110 (2.6)	263 (6.1)
Anal/Genital	106 (2.5)	134 (3.1)
Other	102 (2.4)	129 (3.0)
Neck	72 (1.7)	366 (8.5)
Most Exposed Areas	62 (1.4)	76 (1.8)
Ears	47 (1.1)	76 (1.8)
Eyes	24 (0.6)	36 (0.8)
Only under clothes	17 (0.4)	27 (0.6)
Nose	3 (0.1)	3 (0.1)
Erythroderma	2 (0.1)	3 (0.1)

*Excludes 8 with no primary site listed.
†Total of any of up to 3 sites or up to 3 diagnoses listed.
‡Excludes 23 patients with no primary final diagnosis.

Warshaw EM et al. North American Contact Dermatitis Group Patch Test Results for 2009-2010. DERMATITIS. March/April 2013. Vol 24 2:50-59

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Dermatitis with Scattered Generalized Distribution

- Allergic Contact Dermatitis with generalized distribution
- Systemic Contact Dermatitis
  - Contact sensitized → exposed orally, transcutaneously, IV or inhalation → generalized (or localized) dermatitis

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Dermatitis with Scattered Generalized Distribution

Two most common allergens:

Nickel

Estimated SCD following oral nickel in nickel allergic patients

- 1% to 0.3 - 0.6 mg/d (normal diet)
- 10% to 0.55 - 0.89 mg of nickel
- ~ 50% to 2.5 mg nickel

Approximate nickel content of foods

- Soybean, ~ 1 cup: 895mcg
- Figs ~5: 85 mcg
- Cocoa, 1 tbsp: 147 mcg
- Lentils ½ cup cooked: 61 mcg
- Cashew, ~ 18 nuts:143 mcg
- Raspberry: 56 mcg
- Vegetables, canned ½ cup: 40 mcg
- Lobster 3 oz: 30 mcg
- Oat Flakes 2/3 cup: 25 mcg
- Peas Frozen, ½ cup: 27 mcg

Balsam of Peru

~ half of patients with (+) PT to MP who followed a low BOP diet had their dermatitis improve

Foods to Avoid in Balsam-Restricted Diet

- Citrus fruits: oranges, lemons
- Flavorings: pastries, bakery goods
- Spices: cinnamon, cloves, vanilla, curry, allspice, anise, ginger
- Spicy condiments: ketchup, chili
- Perfumed or flavored tea & tobacco
- Chocolate
- Ice cream
- Cola, spiced soft drinks
- Tomatoes

Zug KA, Rietschel RL, Warshaw EM, et al. The value of patch testing patients with a scattered generalized distribution of dermatitis: Retrospective cross-sectional analyses of North American Contact Dermatitis Group data, 2001 to 2004. J Am Acad Dermatol 2008;59:426-431

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SUMMARY STATEMENT: The clinician should recognize that contact sensitization to metals or bone cement used in orthopedic, cardiac, other surgical, dental, and gynecological implants have been associated with cutaneous and non-cutaneous presentations (including localized pain, swelling, erythema, warmth, implant loosening, decreased range of motion, or stent stenosis or pericardial effusions in the case of cardiac implants).

Nickel in Biomedical Devices

Reports of dermatitis to biomedical devices lead to:

- Consultation requests regarding safety of metal medical devices in nickel-sensitized patients
- High variability of care in terms of testing & recommendations
- Increased health care costs
- Medico legal concerns contribute to testing consultations
- Selection of more expensive & less durable option

As nickel allergy incidence increases, this problem also presumably will increase

Komik R and Zug K. Dermatitis2008;19(1):3-8

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"Does sensitization begin in infancy?"

- Nickel: most common (+) allergen in asymptomatic children
  - 12.9% of children (6- 67.5 mos) were (+) to nickel

Risk factors for development of nickel allergy

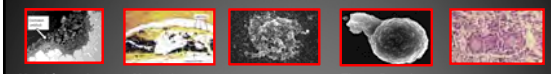
- Body piercing (most important)
  - Sensitization in pierced ears (14.8%) vs. unpierced (1.8%)
- Number of piercings
  - 4% (+) PT in unpierced males
  - 11.1% with 1 piercing
  - 14.6% with multiple piercings*

Lessons from this well-documented epidemiology of nickel sensitization

Kütting et al recommend to delay ear piercing until after 10 y.o. (presumably to allow for development of immune tolerance)

Bruckner AL, Weston WL, Morelli JG. Does sensitization to contact allergens begin in infancy? Pediatrics 2000;105:e3
Kütting B, Brehler R, Traupe H. Allergic contact dermatitis in children: strategies of prevention and risk management Eur J Dermatol 2004;14:80–5 Kütting B, Brehler R, Traupe H. Allergic contact dermatitis in children: strategies of prevention and risk management Eur J Dermatol 2004;14:80–5
*Erlich A, Kucenic M, Belsito D. Role of body piercing in the induction of metal allergies. Am J Contact Dermat 2001;12:151–155

Pathophysiology of Metal Allergy and Implant Failure



Metal Corrosion | Metal tissue Deposition | Necrosis | Tissue Reactions | Phagocytosis | Foreign body giant cells

Immunologic Level

- Endothelial cell exposure induce intercellular adhesion molecule1 *e*xpression
- Cutaneous reactions above implant are primarily T cell-mediated type IV rxns
- Tissues adjacent to implant in metal sensitive patients have elevated immune cells/markers (CD3þ T lymph, CD4þ cells, CD11cþ macrophages/dendritic cells & cells with abundant MHC class II)

Watari F et al. J. R. Soc. Interface 2009;6:S371-S388
Cunningham et al. The effect of spinal instrumentation particulate wear debris - an in vivo rabbit model and applied clinical study of retrieved instrumentation cases. The Spinal Journal. 2003; 3:1. 19–32
Basko-Plluska J et al. Cutaneous and Systemic Hypersensitivity Reactions to Metallic Implants. Dermatitis. 2011. 22: 65–79
Schalock1, et al *Hypersensitivity reactions to metallic implants – diagnostic algorithm & suggested patch test series for clinical use. Contact Dermatitis, 66, 4–19*

Orthopedic Implant Allergy

- 5% of orthopedic implant & up to 21% of patients with preop metal sensitivity may develop cutaneous allergic reactions on reexposure to the same metal
- Clinical manifestations
  - Cutaneous
    - localized: eczematous reaction overlying implant (urticaria & vasculitis reported)
    - generalized
    - both
- Non Cutaneous Reactions
  - Implant Failure

Basko-Plluska JL, Thyssen, JP & Schalock PC. Cutaneous & Systemic Hypersensitivity Reactions to Metallic Implants.Dermatitis. 2011;22:65–79
Niki Y, Matsumoto H, Otani T, et al. Screening for symptomatic metal sensitivity: a prospective study of 92 patients undergoing total knee arthroplasty. Biomaterials 2006;26:1019–26

Prospective Longitudinal Studies and Reviews

Study	Pt	Conclusions
Carlsson & Mo¨ller 1989	18	**Metal allergic pts with confirmed allergy** to metal in their device prior to stainless steel orthopedic implants **had no issues (6-yr ff-up)**
Thyssen et al, 2009	356	**Risk of surgical revision not increased in patients with metal allergies**
Niki et al 2006	**92**	**26% had (+) LST tests to at least oe metal (Ni, Co, Cr, Fe) 5% of total study developed cutaneous allergic reactions In metal (+) prior to implant: 21% developed dermatitis at site of implant (some widespread)**
Eben et al 2010	**92**	**66/92 had sx (pain, reduced motion, swelling) Rates of allergy: nickel: 24.2% vs 3.8% (no Sx); cobalt: 6.1%; vs 3.8% Symptomatic (31.8%) had allergic reaction to bone cement components**
Braathen et al	**16**	**81% of failed metal-on-metal implants had metal sensitivity (PT &/or LTT)**
Hallab N, et al 2001		**Accumulated reports in total hip arthroplasty: prevalence of metal allergy ~ 25% in well-functioning vs. ~ 60% in failed/poorly functioning implant**

Carlsson A, Mo¨ller H. Implantation of orthopaedic devices in patients with metal allergy. Acta Derm Venereol 1989;69:62–6
Thyssen JP, Jakobsen SS, Engkilde K, et al. The association between metal allergy, total hip arthroplasty, and revision. Acta Orthop 2009;80:646–52
Merritt K, Rodrigo JJ. Immune response to synthetic materials.Serialization of patients receiving orthopaedic implants. Clin Orthop 1996;326:71–9
Niki Y, et al. Screening for symptomatic metal sensitivity: a prospective study of 92 patients undergoing total knee arthroplasty. Biomaterials 2006;26:1019–26.
Eben R, et al. Contact allergy to metals and bone cement components in patients with intolerance of arthroplasty. Dtsch Med Wochenschr. 2010;135:1413–22.
Thomas P, et al. Increased metal allergy in patients with failed metal-on-metal hip arthroplasty & perimplant T-lymphocytic inflammation. Allergy 2009;64:1157–65
Hallab N, Merritt K, Jacobs JJ. Metal sensitivity in patients with orthopaedic implants. J Bone Joint Surg Am 2001;83:428–36.

Allergic Contact Dermatitis from bone cement components

Reported in 24.8% of patients (n = 239)*

Common Bone Cement Allergen in Total Joint Arthroplasties	Use	Approx % (+) Reaction
N,N-dimethyl-p-toluidine (DPT)	**Reaction initiator**	**10**
Polymethyl methacrylate (MMA)	**Cement Base**	**25**
Benzoyl Peroxide	**Activator**	**8-10**
Hydroquinone	**MMA Stabilization**	**5**
Gentamycin	**Antibiotic**	**17-24**

Common causes of failure:
infection, recurrent dislocation, aseptic osteolysis, fractures

Thomas P, Schuh A, Eben R, et al. Allergy to bone cement components. Orthopa¨de 2008;37:117–20
Haddad FS, Cobb AG, Bentley G, et al. Hypersensitivity in aseptic loosening of total hip replacements. The role of constituents of bone cement. J Bone Joint Surg Br 1996;78:548–9
Kuehn KD, Ege W, Gopp U. Acrylic bone cements: composition and properties. Orthop Clin North Am 2005;36:17–28

Endovascular stent & In-stent restenosis

Study		Positive Findings	Negative Findings
Köster R, et al 2000 Prospective study	Coronary in-stent restenosis 6 mos post stent & PT 2 mo after angioplasty	(+) PT in 10/131 (8%) - All 10 (100%) had in-stent restenosis	However, 57% of (-) PT had ISR
Iijima R, et al 2005 Prospective study	174 stented patients -109 (initial placement) - 65 (restenosis)	Recurrence of ISR: higher (+) PT to metals (39% vs.12%; p =0.02) Predictors of recurrent restenosis: (+) patch test (OR 4.39, p =0.02)	Initial stent implantation not significantly different between with or w/o restenosis (10% vs 9%)
Thyssen, et al 2012 Linkage Study	149/18,794 (0.8%) PT prior to metal stent placement		14% (21/149) had ISR - **Only 11.8% (2 /21) had metal allergy**

Gold-plated stents (thought to be inert), subsequently showed that gold in cardiac stents was a strong risk factor for ISR, especially in those with prior gold allergy *

Köster R, Vieluf D, Kiehn M, et al. Nickel and molybdenum contact allergies in patients with coronary in-stent restenosis Lancet 2000;356:1895–7
Iijima R et al. The impact of metallic allergy on stent implantation: metal allergy & recurrence of in-stent restenosis. Int J Cardiol 2005;104:315–25
Thyssen J.P et al. G H No association between metal allergy and cardiac in-stent restenosis in patients with dermatitis – results from a linkage study. *Contact Dermatitis* 2011; 64: 138–147.
*Svedman C et al. A correlation found between contact allergy to stent material and restenosis of the coronary arteries. *Contact Dermatitis* 2009: 60: 158–164

Pacemakers/Defibrillators

- Majority of reactions are infections
- Allergic complications rare: ~30 cases reported in literature
  - Ti alloy shell: most frequent
  - Manifestations:
    - dermatitis localized above implant
    - impaired wound healing
    - generalized or remote dermatitis (uncommon)

Schalock et al Hypersensitivity reactions to metallic implants – diagnostic algorithm and suggested patch test series for clinical use. *Contact Dermatitis*, 66, 4–19
Honan D, et al. Hypersensitivity reactions associated with endovascular devices. *Contact Dermatitis* 2008: 59: 7–22
Hallab N J, Jacobs J J. Biologic effects of implant debris. *Bull NYU Hosp Jt Dis* 2009: 67: 182–188
Oprea M L, Schri oring H, Sachweh J S, Ott H, Bertz J, Vazquez-Jimenez J F. Allergy to pacemaker silicone compounds: recognition and surgical management. *Ann Thorac Surg* 2008: 87: 1275–1277

Dental Implants & Orthodontic Devices

- Potential allergen groups
  - Ni–palladium &/or Ti alloys
  - CoCrMo alloys
  - Epoxy & epoxy-acrylate preparations
  - Anesthetics & flavorings
- Flexible titanium-nickel arch wires release more nickel compared to stainless steel
  - Nickel: most common contact allergen to orthodontics

Schalock1, et al Hypersensitivity reactions to metallic implants – diagnostic algorithm and suggested patch test series for clinical use. *Contact Dermatitis, 66, 4–19*

SUMMARY STATEMENT: **Consider pre-operative evaluation for metal sensitization in patients with a significant history of metal allergy.**

- Indication for pre-op patch testing in patients with a history of metal allergy is still controversial at this time
- However, some studies that show that patients with a high suspicion of metal allergy who underwent pre-operative patch testing that guided the selection of the implant, have shown improved outcomes. (Sood MD, Arch Dermatol 2012; Schalock PC Contact Dermatitis 2012)

Sood MD, Arch Dermatol 2012
Schalock PC Contact Dermatitis 2012

Should allergy screening be performed?

- Patients with no history of metal hypersensitivity need not be screened prior to implantation
- Pre-implantation PT identifies metal-allergic individuals*
  - Screening prior to surgery is recommended for those with history of metal sensitivity of a magnitude sufficient to cause concern to the patient or healthcare provider **
- Post-implantation PT: joint pain, implant loosening, or unexplained cutaneous reaction at the implant site with a question of metal hypersensitivity

Schalock1, et al. Hypersensitivity reactions to metallic implants – diagnostic algorithm & suggested patch test series for clinical use. *Contact Dermatitis*, 66, 4–19
*Reed K B, et al. Retrospective evaluation of patch testing before or after metal device implantation. *Arch Dermatol* 2008; 144: 999–1007
** Thyssen JP, Menné T, Schalock P C, Taylor J S, Maibach H I. Pragmatic approach to the clinical work-up of patients with putative allergic disease to metallic orthopaedic implants before and after surgery. *Br J Dermatol 2011*; 164:473–478

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SUMMARY STATEMENT: The clinical relevance of commercially available blood tests to diagnose metal sensitization have not been determined

Patch Testing vs. Lymphocyte Transformation Test

- *Measures lymphocyte proliferation* (stimulation index) after 7 days incubation +/- allergen
  - Limited allergens, availability & rapid decay of T cells (rapid transportation) ·
- ? LTT better reflect immune reactions within the body, whereas PT reflects cutaneous reactivity
- May be useful in questionable cases
  - 54/56 patients with Ti implants, (-) PT & (+) Ti LTT whose systemic symptoms resolved after implant removal
- Needs Validation

Lymphocyte Toxicity Assay (Health Diagnostics and Research Institute, South Amboy, NJ)
Muller K E, Valentine-Thon E. Hypersensitivity to titanium: clinical & laboratory evidence. *Neuro Endocrinol Lett* 2006; 27: 311–313

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What to test with

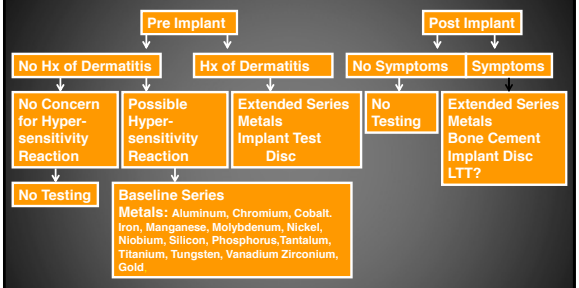
PT with limited allergens is not recommended as there may be multiple causes of the dermatitis

- **Baseline series** [NACD, ACDS, European Baseline Series etc]
- **Extended series & specialty trays**
  - Extended NA standard series (Chemotechnique or Allergeaze; SmartPractice, Calgary,AB,Canada)
  - International Comprehensive Baseline series (Chemotechnique)
- **Metals**

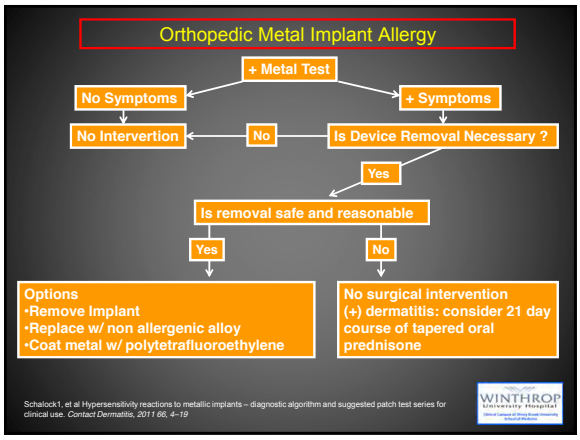
Schalock1, et al Hypersensitivity reactions to metallic implants – diagnostic algorithm and suggested patch test series for clinical use. *Contact Dermatitis, 2011*. 66, 4–19

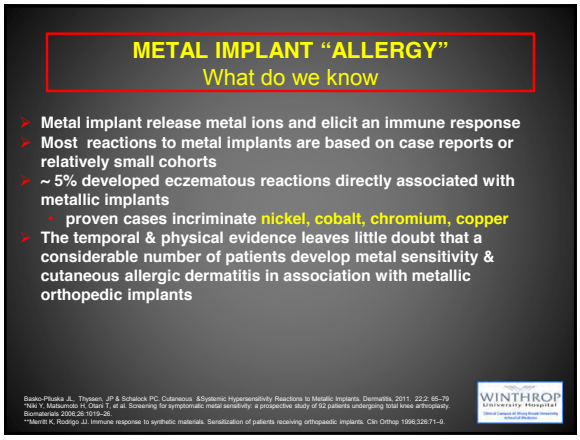
Schalock1, et al Hypersensitivity reactions to metallic implants – diagnostic algorithm and suggested patch test series for clinical use. *Contact Dermatitis*, 2011, 66, 4–19

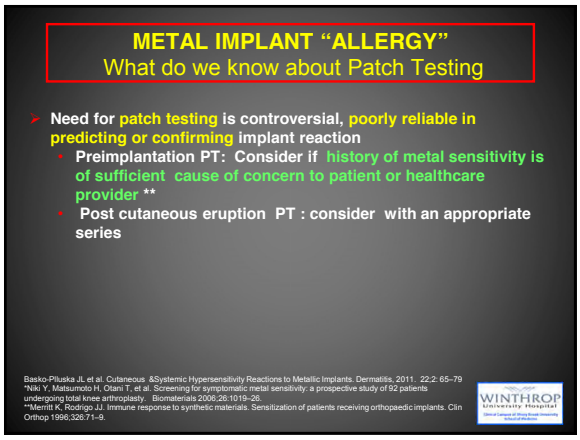
Suspect Orthopedic Metal Implant Allergy



Schalock1, et al Hypersensitivity reactions to metallic implants – diagnostic algorithm and suggested patch test series for clinical use. *Contact Dermatitis, 2011* 66, 4–19


Orthopedic Metal Implant Allergy
+ Metal Test
No Symptoms
+ Symptoms
No Intervertion
No
Is Device Removal Necessary ?
Yes
Is removal safe and reasonable
Yes
No
Options
•Remove Implant
•Replace w/ non allergenic alloy
•Coat metal w/ polytetrafluoroethylene
No surgical intervention
(+) dermatitis: consider 21 day course of tapered oral prednisone
Schalock1, et al Hypersensitivity reactions to metallic implants – diagnostic algorithm and suggested patch test series for clinical use. Contact Dermatitis, 2011 66, 4–19
WINTHROP University Hospital


METAL IMPLANT "ALLERGY"
What do we know
Metal implant release metal ions and elicit an immune response
Most reactions to metal implants are based on case reports or relatively small cohorts
~ 5% developed eczematous reactions directly associated with metallic implants
proven cases incriminate nickel, cobalt, chromium, copper
The temporal & physical evidence leaves little doubt that a considerable number of patients develop metal sensitivity & cutaneous allergic dermatitis in association with metallic orthopedic implants
Basko-Pluska JL. Thyssen, JP & Schalock PC. Cutaneous &Systemic Hypersensitivity Reactions to Metallic Implants. Dermatitis, 2011. 22:2: 65–79
*Niki Y, Matsumoto H, Otani T, et al. Screening for symptomatic metal sensitivity: a prospective study of 92 patients undergoing total knee arthroplasty. Biomaterials 2006;26:1019–26.
**Merritt K, Rodrigo JJ. Immune response to synthetic materials. Sensitization of patients receiving orthopaedic implants. Clin Orthop 1996;326:71–9.
WINTHROP University Hospital


METAL IMPLANT "ALLERGY"
What do we know about Patch Testing
Need for patch testing is controversial, poorly reliable in predicting or confirming implant reaction
Preimplantation PT: Consider if history of metal sensitivity is of sufficient cause of concern to patient or healthcare provider **
Post cutaneous eruption PT : consider with an appropriate series
Basko-Pluska JL et al. Cutaneous &Systemic Hypersensitivity Reactions to Metallic Implants. Dermatitis, 2011. 22:2: 65–79
*Niki Y, Matsumoto H, Otani T, et al. Screening for symptomatic metal sensitivity: a prospective study of 92 patients undergoing total knee arthroplasty. Biomaterials 2006;26:1019–26.
**Merritt K, Rodrigo JJ. Immune response to synthetic materials. Sensitization of patients receiving orthopaedic implants. Clin Orthop 1996;326:71–9.
WINTHROP University Hospital

METAL IMPLANT "ALLERGY"
What else do we know

- (-) PT is reassuring for absence of delayed hypersensitivity
- A (+) PT does not prove relevance
- If relevant allergens are identified & corticosteroid therapy is insufficient to clear eruption, removal of implant may be considered

What we do **NOT** know about Metal Implant Allergy

- Whether risk of allergic reaction to orthopedic implants increase in metal sensitized individuals
- Whether supposed allergies to implanted devices really cause problems such as loosening or dermatitis
- How to identify the subgroup of metal allergic patients with increased risk of complications from metal implant
- Whether PT can truly detect reactions to implanted devices
- Patch Testing vs. Lymphocyte Transformation Test

Based on the complex findings, it is difficult to make general principles for good clinical practice & prospective longitudinal studies are strongly needed

Patch Testing:
the only way to diagnose Allergic Contact Dermatitis

- The greatest abuse of the Patch Test is failure to use the test Colman, 1982
- Relief of symptoms average 143 days sooner on patch tested vs. non patch tested patients
  RajagopalanR et al. Cutis 1996;57:360-364

Patch Me if You Can!

TRUE TEST vs. NACDG

Of the top 40 NACDG allergens, the following antigens are not on TRUE Test:

- Fragrance mix II (fragrance) (4.7%)
- Iodopropynyl butylcarbamate (preservative) (4.3%)
- Propylene glycol (humectant & stabilizer) (3.2%)
- Propolis (excipient) (2.1%)
- Dimethylaminopropylamine (surfactant) (2.0%)
- Hydroxyethyl methacrylate (2.0%)
- Oleamidopropyl dimethylamine (surfactant) (1.8%)
- Shellac (eye or lip products) (1.7%)
- Decyl glucoside (surfactant) (1.5%)
- Cocamidopropyl betaine (surfactant) (1.4%)
- Majantole (flavoring/fragrance) (1.4%)
- ylang ylang oil (flavoring/fragrance) (1.3%)
- carvone (flavoring/fragrance) (1.1%)
- DMDM hydantoin (preservative) (1.0%)
- Mixed dialkyl thioureas (rubber manufacturing) (1.0%)

(%) frequency of positive reaction in NACD 2009-2010

Warshaw EM et al. North American Contact Dermatitis Group Patch Test Results for 2009-2010. DERMATITIS, March/April 2013. Vol 24: 2:50-59

Delayed Patch Test Reactions after 5 Days

- Metals
  - Gold
  - Potassium Dichromate
  - Nickel
  - Cobalt
- Topical Antibiotics
  - Neomycin
  - Bacitracin
- Topical Corticosteroids
- PPD

Davis M et al. Delayed Patch Test reading after 5 days : the Mayo Clinic Experience. JAAD Aug 2008; 59 (2):225-233

Recommendation Prior to Patch Testing
"Lo.C.A.L. (Low contact allergen) Skin Diet (Zug KA)

Eliminates most common allergens:

- Fragrance
- Formaldehyde Releasing Preservatives
- MCI/MI
- MDG/PE
- Lanolin
- CAPB
- Benzophenone-3

- Cover girl clean fragrance free liquid make-up
- Clinique blushing blush powder blush
- Clinique soft pressed eye shadow
- Max factor vivid impact lip liner-all shades
- Almay hypoallergenic roll-on anti-perspirant/ deodorant
- Cerave moisturizing lotion/ vanicream
- Cetaphil gentle skin cleanser
- Free & Clear shampoo
- Free & Clear hair spray - firm hold

Topical Skin Care Product Databases

Compliance with allergen avoidance is frequently difficult. After PT, patients can be provided a comprehensive list of skin care products that are free of their identified allergens

1. Contact Allergen Management Program (CAMP)
.American Contact Dermatitis Society: info@contactderm.org

Allergists who need reference from ACDS member, send CV:
Luz Fonacier, MD. Head of Allergy Winthrop University Hospital
Professor of Clin Medicine, SUNY at Stony Brook
lfonacier@winthrop.org

2. Contact Allergen Replacement Database (CARD)
Created by James A. Yiannias, MD at the Mayo Clinic